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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,249	01/28/2004	John R. Stuelpnagel	01-00009	4783

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EXAMINER	
BAUGHMAN, MOLLY E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/767,249	STUELPNAGEL ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 29-51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 29-51 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 28 January 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/9/06; 9/13/04; 3/15/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Objections/ Informalities

a. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The invention is drawn to a method of making and using composite arrays for the detection of a plurality of target analytes; it is suggested that this be reflected in an amended title.

2. Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 and 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 32 is confusing because it is unclear how the claim is further limiting. The multiplex PCR amplification described is not mentioned in the claims it depends upon and it is unclear how this step correlates with its method.

b. Claims 49-51 are confusing because it is unclear how "96 wells" are a method. The claims only refer to a method and do not distinctly point out the role of the wells (96, 384, or 1536) within the method upon which it depends. It is suggested to modify the claims to describe the product (i.e. wells) for use in the method, instead of being the method.

3. Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 29, 30, 34, 38-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor, et al (U.S. 5,324,633, 1994).

Regarding claims 29, 30, and 34, Fodor et al describe a method for determining the binding affinity of a receptor to a surface-bound, high density ligand array and vice versa (ligand bound to receptor) (page 1, lines 7-11). The ligands (proteins, nucleic acids, peptides, etc (page 3, lines 1-9)) are formed on a substrate (from wells, to beads on the surface page 5, lines 5-17)) at predetermined locations (page 1, lines 65-68). Several substrates, each having a common group of polymers synthesized thereon, are exposed to the receptors (microorganism receptors, enzymes, antibodies, polypeptides, nucleic acids, etc. (page 4-5)) simultaneously through flow cells including a plurality of reservoirs (page 12, lines 4-12) (i.e. dipping). Binding affinity is determined via surface fluorescence intensity (throughout document).

Regarding claims 38, Fodor et al disclose different ligands directly attached to a substrate on separate regions of the surface, for example, wells, raised regions, etched trenches, or the like.

Regarding claim 39, Fodor et al also disclose in another embodiments, smalls beads (i.e., microspheres) with ligands on the surface of the substrate (page 5, lines 5-12).

Regarding claims 40-44, Fodor et al disclose the receptor marked with a fluorescent label, such as a fluorescein tag, and the fluorescence intensity data provides a means to measure the receptor binding to the surface-bound ligands (page 2, lines 1-16 and page 6, lines 25-61). According to the instant specification, fluorescent dyes can also serve as decoder binding ligands, as in claim 40. A confocal microscope is used to measure the fluorescent light intensity along the surface of the substrate (page 10, lines 44-56).

Regarding claim 45, Fodor et al describe extracting quantitative information regarding the binding affinity of the receptor to various ligand substrates based on the fluorescence intensity data for solutions of varying concentrations of receptors (page 2, lines 9-13 and page 10, lines 24-36).

4. Claims 29, 34-38, 40-45, and 48-51 are rejected under 35 U.S.C. 102(e) as being anticipated by Burbaum et al (U.S. 5,876,976, 1999).

Regarding claims 29, and 41-45 Burbaum et al. disclose a solid support, which can be the bottom of a microtiter plate, coated with a target molecule, and then exposed

to labeled ligand (page 9, lines 18-27). The fluorescently labeled ligand in solution is contacted with the solid support, which can be beads containing 10^6 binding sites per bead (page 6, lines 18-21 and 44-47). Target molecules can be statistically evaluated by placing a plurality of compounds in each assay container (i.e. microtiter plate), and determining the number and potency of each compound (page 10, lines 7-10 and page 8, lines 14-26). Detection is determined via signal created by bound fluorescently labeled ligand (i.e. fluorescein, rhodamine, texas red – page 8, lines 61-67) to the target molecule (page 8, lines 46-61).

Regarding claim 34, Burbaum et al disclose a solid support coated with any desired target including: peptides, antibodies, DNA-binding proteins, oligonucleotides, etc. (page 6, lines 61-67, and pages 7-8).

Regarding claims 35-37, Burbaum et al describe the use of beads as a solid support, typically containing 10^6 binding sites per bead, and beads at preferred density of 100 to 1000 per sample volume (page 6, lines 18-21, and page 8, lines 26-44).

Regarding claim 38, Burbaum et al also describe a method wherein the antibody (i.e. a bioactive agent) is directly coated onto the microbeads and suspended in a solution of target analytes (pages 7-8, lines 59-67, and lines 1-7 respectively).

Regarding claim 40, Burbaum et al disclose target analytes, in this case a library of compounds, with a chemical tag to enable the identification of the target analyte via decoding the tag (pages 9-10, lines 57-67, and 1-4 respectively).

Regarding claims 48-51, Burbaum et al disclose the invention being performed in a microtiter plate, wherein the method can be carried out in 96-well, 384-well, or 1536-well microtiter plates (page 8, lines 14-25).

5. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fodor et al (U.S. 5,324,633, 1994) in view of Fodor et al (U.S. 5,800,922, 1998).

The teachings of the primary reference are discussed above, including the methods as claimed in the instant claims 30, 34, 38-45. However, Fodor et al do not teach a method comprising nucleic acids with single nucleotide polymorphisms (SNPs)

as in claim 31. Fodor et al do not teach multiplexing said nucleic acids with SNPs in PCR amplification and subsequent binding to said bioactive agents as in claim 32. Fodor et al do not teach a method wherein the nucleic acids comprising SNPs are labeled with fluorochromes during PCR amplification, as in claim 33. Fodor et al do not teach a method wherein the array locations comprise from 10,000,000 to about 2,000,000,000 bioactive agents per square centimeter (claim 35), or 100,000 to about 10,000,000 bioactive agents per square centimeter (claim 36), or 10,000 to about 100,000 bioactive agents per square centimeter (claim 37). Fodor et al. also do not teach the method further comprising quantitating a specific mRNA (claim 46), or quantitating a specific mRNA in the presence of total cellular mRNA (claim 47).

Regarding claim 30-34, Fodor et al (1998) disclose a method of producing a substrate having a plurality of positionally distinguishable sequence specific reagents, wherein the reagents could be polynucleotides, polymers, carbohydrates, polypeptides, etc. (page 2, lines 34-67, and page 6-7, lines 63-67; 1-5). The methods can also be coupled to a polymerase chain reaction (page 27, lines 17-19, and page 58, lines 23-26), wherein specific reagents (probes) can be used to detect one or more mismatched bases in a fluorescently labeled target (page 69, lines 17-67, page 4, lines 45-64). It would have been obvious to one of ordinary skill in the art at the time of the claimed invention to apply the detection of mismatched bases (i.e. single nucleotide polymorphisms) within a fluorescently labeled target as taught by Fodor et al (1998) to the method of dipping an array, containing a plurality bioactive agents, into a second substrate of target analytes, as taught by Fodor et al (1994). The skilled artisan would

have had a reasonable expectation of success in adding the detection of SNPs in target nucleic acids to the method of Fodor et al (1994). It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed detection of SNPs in target nucleic acids therein.

Regarding claims 35-37, Fodor et al (1998) disclose a method of generating the desired repertoire of oligonucleotide probes on a substrate, wherein the densities could range from 5 regions/cm^2 to an excess of one million regions/ cm^2 (page 20, lines 13-37). It would have been obvious to one of ordinary skill in the art at the time of the claimed invention to apply the varying densities of bioactive agents at array locations by Fodor et al (1998) to the method of dipping an array, containing a plurality bioactive agents, into a second substrate of target analytes, as taught by Fodor et al (1994). The skilled artisan would have had a reasonable expectation of success in adding the various bioactive agent densities at array locations to the method of Fodor et al (1994). It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the various bioactive agent densities at array locations therein.

Regarding claim 39, Fodor et al (1998) disclose the use of microspheres (beads) containing a plurality of coded substrates to indicate the sequence specificity of said reagent (page 4, lines 1-4 and page 45-46).

Regarding claims 40-44, Fodor et al (1998) disclose the use of using different labels to detect each target simultaneously, wherein one target could be labeled with a green fluorescent label and a second target a red fluorescent label. A wide variety of

fluorescers may be employed (i.e. a chromogen), and can be detected by analyzing the differences in optical signals (page 52-53). In a different labeling application, coding information can be incorporated on molecules such as nucleic acids, which can be amplified through PCR, and then later decoded (page 58, lines 11-44).

Regarding claims 45-47, Fodor et al (1998) disclose characterizing various samples by testing their mRNA sequence intent (page 29, lines 33-36, and 42-46). Furthermore, they discuss defining the pattern of expression of mRNA, in comparison to other types of RNA, wherein different levels of RNA may be found in correlation to the developmental stage of the cell (page 30, lines 10-20). One of ordinary skill in the art would have been motivated to modify the method of Fodor et al. (1994) to quantitate the differences in levels of specific mRNA in the presence of total cellular mRNA because the benefits of quantitating various types of mRNA were shown by Fodor et al (1998). The skilled artisan would have had a reasonable expectation of success in adding the quantification of specific mRNA levels in the method of Fodor et al (1994). It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed quantification of specific mRNA levels therein.

6. Claims 30-33, 38,and 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fodor et al (U.S. 5,324,633) as applied to claims 29, 30, 34, 38-45 above, and further in view of Guo et al.

The teachings of the primary reference are discussed above, including the methods as claimed in the instant claims 30-33, 38, and 41-45. However, Fodor et al do not teach a method comprising nucleic acids with single nucleotide polymorphisms (SNPs) as in claim 31. Fodor et al do not teach multiplexing said nucleic acids with SNPs in PCR amplification and subsequent bring to said bioactive agents as in claim 32. Fodor et al also do not teach a method wherein the nucleic acids comprising SNPs are labeled with fluorochromes during PCR amplification, as in claim 33.

Guo et al. teach a similar method, wherein a plurality of allele-specific oligonucleotides (ASOs) are each directly coupled at a specific spot on an array surface (page 5457, 1st and 3rd paragraph). Target cDNA and genomic DNA samples are first submitted to PCR amplification with allele-specific fluorescently labeled primers (page 5457, 2nd col.). The fluorescein-labeled single-stranded PCR products are then bound to the array of ASOs under specialized hybridization conditions and provide a means to discriminate between matches and mismatches for all polymorphisms analyzed (page 5458, 2nd col., 1st paragraph). Detection occurs through quantitative analysis of the fluorescence image, and the amount of fluorescent light emitted from each spot is representative of the amount of labeled DNA associated with that spot (page 5462, 2nd col.).

One of ordinary skill in the art would have been motivated to modify the method of Fodor et al. to use targets of nucleic acids, comprising single nucleotide polymorphisms, which are fluorescently labeled via PCR prior to binding to bioactive agents because the benefits of detecting SNPs via multiplexing PCR with allele-specific

oligonucleotide arrays were shown by Guo et al. The skilled artisan would have had a reasonable expectation of success by adding the detection of PCR amplified nucleic acids comprising SNPs in the method of Fodor et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed PCR amplified nucleic acids comprising SNPs therein.

7. Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 29-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, and 9 of U.S. Patent No. 6,858,394. Although the conflicting claims are not identical, they are not patentably

distinct from each other because the patent and instant claims are drawn to a genus:species relationship. For example, the patent claims 1 and 9 recite contacting one or more samples within a first substrate comprising a plurality of assay locations to a second substrate comprising a plurality of array locations, which further comprises a population of microspheres distributed at discrete sites. The instant claim 29 recites dipping a second substrate comprising a plurality of array locations, containing a plurality of discrete sites with different bioactive agents, into a first substrate comprising a plurality of assay wells with a plurality of target analytes and dependent claim 39 recites microspheres, containing bioactive agents, associated with the array locations. The patent claims are drawn to the term "contacting" and according to its specification, this also entails the instant claim's term of "dipping." Therefore, the instant claims are obvious in the view of the patent claims since they relate as species and genus, respectively.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
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MEB 7/6/06

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